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IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF	:
MARIE-CLAUDE GINGRAS, ET AL.	: EXAMINER: BELYAVSKYI
SERIAL NO: 10/021,509	:
FILED: DECEMBER 7, 2001	: GROUP ART UNIT: 1644
FOR: TREM-1 SPLICE VARIANT FOR USE IN MODIFYING IMMUNE RESPONSES	:

PETITION FOR REHEARING

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

SIR:

This petition is submitted within the two month period in response to the Decision on Appeal dated March 31, 2008. The Appellants have reasons to believe from the report of the Decision on Appeal that there was severe misapprehensions by the Board on arguments presented by Appellants. This request presents the points misapprehended and provides the relevant explanations in response to the Decision on Appeal.

REAL PARTY OF INTEREST

The real party of interest herein is GenePrint Corporation, Houston, Texas.

RELATED APPEALS AND INTERFERENCES

Appellants are not aware of any related appeals and/or interferences to the present case.

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STATUS OF CLAIMS

Claims 1, 3, 5, 11, 15, 16 and 40-42 are active in this application, are rejected and appealed in a petition for a Rehearing. After the Hearing of March 6, 2008, the rejection of claims 1, 3, 5, 11, 15, 16, and 40-42 under 35 U.S.C. § 112 first paragraph, as drawn to new matter, is reversed. The rejection of claims 1, 3, 5, 11, 15, 16, and 40-42 under 35 U.S.C. § 102(e), as anticipated by Wang is reversed. The rejection of claims 1, 3, 5, 11, 15, 16, and 40-42 under 35 U.S.C. § 112 first paragraph, as lacking enablement, is affirmed. The rejection of claims 1, 3, 5, 11, 15, 16, and 40-42 under 35 U.S.C. § 102(e) as anticipated by Reuben is affirmed.

STATUS OF AMENDMENTS

There are no outstanding amendments in this case as all amendments previously filed in response to the October 21, 2005 Official Action have been entered for the purpose of this Appeal (Advisory Action mailed August 24, 2006).

SUMMARY OF CLAIMED SUBJECT MATTER

The invention currently under examination is to a method of modulating an immune response comprising administering to an animal, in need thereof, a composition of soluble polypeptides with at least a portion of amino acids 1 to 136 of SEQ ID NO:2 or a polypeptide mimetic thereof, in an amount effective to modulate the levels of TREM-1 and /or ligand binding activity whereby the immune response is modulated in the animal.

Claim 1 is supported on pages 4-7, pages 11, 12, page 19, figures 1 and 4 of the specification as originally filed. Claim 40 is supported at paragraph [0033] in the specification. Claim 41 is supported by Example 11. Claim 42 is supported at paragraph [0031].

As discussed in the present Specification, TREM-1 is a receptor of activation on macrophages. TREM-1 includes a soluble extracellular domain and a hydrophobic transmembrane domain (see Fig. 1) that when triggered by its ligand, the ligated complex induces macrophage activation. TREM-1sv is a variant of TREM-1 that is not anchored in the macrophage cell membrane but free to capture TREM-1 ligand. When TREM-1 ligand is captured by TREM-1sv the TREM-1 receptor complex is not triggered and the macrophages are not activated thus permitting the modulation (up or down activation) of macrophages, which in turn modulates the immune response.

GROUNDS TO BE REVIEWED ON REHEARING

A. The first ground of rejection to be reviewed on Rehearing is whether Claims 1, 3, 5, 11, 16, 40 -42 are sufficiently described in the specification so as to be enabled under the meaning of 35 U.S.C. § 112, first paragraph.

B. The second ground of rejection to be reviewed on Rehearing is whether Claims 1, 3, 5, 11, 15, 16, 40 -42 are anticipated by the disclosures of U.S. patent no. 6,420,526 by Reuben under the meaning of 35 U.S.C. § 102(e).

Application No. 10/021,509
Request for Rehearing

ARGUMENTS

A. Claims 1, 3, 5, 11, 15, 16, and 40-42 are enabled by the specification and the knowledge in the art meeting the requirements set forth in 35 U.S.C. 112, first paragraph

Arguments of the Reply Brief are presented first to introduce the contention. Misapprehensions found in the Decision on Appeal are presented and discussed thereafter.

Reply Brief Arguments

As alleged support for this rejection, the Office contends that the specification 1) does not teach how to effectively modulate any immune response, and 2) does not teach how to use an effective amount of the compounds of this invention. This position appears to be based on the lack of a working example in the specification and the belief that practicing the invention would require undue experimentation.

The disclosure for making the composition consistent with the scope of Claim1 can be found on pages 4-7,11-12, 19, Figures 1 and 4 of the specification as originally filed. Based on the specification and the discussion below, it is clear from reading the Specification that the broad scope of the invention as recited in Claim 1 is supported and enabled.

While there is no working examples in the specification, there is sufficient guidance in the Specification and in the art that provide the necessary knowledge for using the claimed methods to effectively modulate an immune response. For example, one need only perfonn the systemic administration of a peptide composition in a dose range between 5 and 50 mg of peptides per kg of body weight as disclosed in Bouchon et al., *Nature* 410:1103, 2001, and Gibot et al., J Exp Med. 200:1419, 2004, (each previously made of record) as recited in the claims to effectively modulate an immune response. In addition, operability of the claimed methods can be predicted by analogy to the art of Bouchon et al. and Gibot et al.

The Examiner's allegation that undue experimentation would be required to practice the claimed invention based on the speculation that the results of the teaching of the present invention are unpredictable are simply not true. Predictability of the claims in regard to a portion of SEQ ID NO: 2 containing binding activities is verified by the work of Gibot et al. and the whole SEQ ID NO:2 by Bouchon et al. both in animals as mentioned above and explained below.

The fact is that there is a relationship between the structure of the TREM-1 molecules that are members of the Ig superfamily and their respective biological activity. In biology, molecules are described by their respective biological activity. In the case of cellular receptors, their respective biological activity relates to their binding sites. The specificity of TREM-1 is that it is a member of the Ig superfamily of cellular receptors as demonstrated by Kelker et al. *J. Mol. Biol.* 342:1237, 2004 and Ibid. *J. Mol. Biol.* 344:1175, 2004 (of record). The members of this Ig family are characterized by having loop domains folding on each others. It has been extensively demonstrated over the last three decades that the binding activity of these Ig superfamily receptor molecules is effected by the binding sites located in these disulfide bounded loop domains (see chapter 16 p. 427-29 of Immunology by H. N. Eisen and see Chapter 7 pp. 7.1 -7.3 of Immunology by I. M. Roitt et al—both of record). Although, the work of Kelker et al. could not identify specifically the exact sequence of the binding site in the loop domain, the work of Kelker et al. has confirmed the structure and presence of these loops domains in the different TREM-1 molecules studied. Therefore, the scientific evidence points out that the binding site activity of TREM-1 is within its loop domain as described in figures 1, 4 and 5 of the present application because of its overall structure and its appertaining to the Ig superfamily of receptors. As cited by Kelker et al. *J. Mol. Biol.* 342:1237, 2004 " TREM-1 (Figure 2(a) and (b), cyan) maintains an overall structure that is homologous to other members of the Ig family," (see page 1240) and "

Comparison of the TREM-1 structure to other members of the Ig-V Type fold demonstrates a close structural relationship." (see page 1239)

The Appellant asserts that the objections raised by the Examiner about protein chemistry and unpredictability of efficacy are purely speculative and in this case are demonstrated to be irrelevant due to the simple peptidic nature of the functional binding site of as mentioned in the specification and demonstrated by Gibot results. Gibot et al. obtained effective immune modulation activity with a small peptide containing only a part of the sequence loop domain being the mouse equivalent peptide of amino acid 103 to 119 of the human sequence (see Figure 4). Thus, compounds having a portion (Gibot et al.), the whole portion or more than the whole portion (Bouchon et al.) of amino acids 36-114 of SEQ ID NO:2 all have a degree of effective immune modulation activity because they contain part of or the whole binding activity site.

As to how to define the dosage, this is routine in the field and certainly cannot be the basis to allege undue experimentation. As mentioned earlier, one can perform the systemic administration of a peptide composition in a dose range between 5 and 50 mg of peptides per kg of body weight as disclosed in Bouchon et al. and Gibot et al as recited in the claims to effectively modulate an immune response. Moreover, as the claimed methods here relate to a therapeutic method some degree of individual variation among patients is inevitable. Medical practitioners routinely prescribe a dose of a therapeutic agent to a patient, observe the response (including any side effects), and modify the dosage or identity of the therapeutic agent depending on the individual patient's response.

The Examiner alleges that the specification does not adequately support that any immune response can be treated with any soluble polypeptide comprising at least a portion of amino acids 1 to 136. The Examiner further basis this assertion because the specification does not provide *in vivo* data. Appellants respectfully submit that the Examiner is incorrect.

The specification clearly asserts that the soluble polypeptides containing the binding site activity can be used to modulate an immune response (e.g., pages 4-7) which is supported by the data discussed in the Declaration of Marie-Claude Gingras, referencing the Bouchon et al publication and the Gibot et al publication noted above. It flows quite clearly from this that the soluble TREM-1 receptor Bouchon et al. utilized, uses the teachings of the present invention to show that a soluble TREM- I receptor inhibits cell functions that are activated by TREM-1 (for example, reduced the activity of TREM-1/DAP12 complex, and reduced inflammation). Thus, the soluble TREM-I receptor of Bouchon et al. was acting as a competitive inhibitor, as described by the present application. Moreover, the use of at least a portion of amino acids 1-136 of SEQ ID NO:2 or a polypeptide mimetic thereof such as the polypeptide utilized by Gibot et al. uses the teachings of the present invention to reduce the inflammation.

Appellants assert that the quantity of experimentation needed to be performed by one skilled in the art to establish fine tuning biological efficacy in humans is merely the domain of the FDA and not relevant to claim the present invention. There is sufficient direction or guidance provided in this application for one skilled in the art to produce the claim composition and to use it to modulate the immune response. The methods outlined in the specification provide sufficient directions to enable the modulation of the immune response by administering a compound that decreases the activity of DAP 1 2/TREM- 1 complex, as illustrated by Bouchon et al. and Gibot et al. In light of the data presented by Bouchon et al. and Gibot et al., Appellants assert that the present invention is enabled since one of skill in the art was able to practice the invention without undue experimentation.

With regards to the Examiner's comment about "How can administering the same amount of the same composition of soluble polypeptide with at least a portion of amino acid 1 to 136 of SEQ ID NO:2 or any polypeptide mimetic thereof simultaneously results in two

opposite effects, i.e. increase or decrease immune response?" The phenomena can be explained. The nature of the pathogenic ligands to be competed on by TREM-1sv is unknown but evidences suggest they are being induced by different types of pathogens such as some bacterial antigens or bacteria released toxins. Depending of the nature of the pathogenic ligands, they could cause either of an overdrive of the immune response by hyper activation of the macrophages through the TREM-1/DAP12 receptors, or can exert an opposite effect by co-activating the macrophages into a suppressive regulatory mode in which they produce suppressive regulatory factors such as interleukin-10 and TGF-B that will paralyze the immune response. Competing such ligands with to block them from reaching the TREM-1 receptors on macrophages can either reduce macrophage hyper activation and therefore allow a down-modulation of the immune response, or can prevent macrophage activation into a suppressive regulatory mode therefore release the immune response from suppression and allowing an up-regulation.

In summary:

1. The mechanisms by which the polypeptide competes for the TREM-1 ligand is described throughout the specification.

2. The structure of different TREM-1 molecules across species have been studied and regardless of their transmembrane region, their ligand binding site is a common conservative region forming a loop binding domain created by a pair of disulfides bridges, one on each end of the loop. (see Kelker et al. and see chapter 16 p. 427-29 of Immunology by H. N. Eisen and see Chapter 7 pp. 7.1 -7.3 of Immunology by I. M. Roitt et al).

3. The enablement of the claimed therapeutic action of the composition having this binding ligand activity is supported by the data in Bouchon et al., and particularly Gibot et al..

4. One can practice the claimed invention because 1) the disclosure for making the composition consistent with the scope of Claim1 can be found on pages 4-7,11-12, 19, Figures 1 and 4 of the specification as originally filed and 2) one can predict the therapeutic efficacy of the composition with TREM-1 ligand activity as long as it contains a portion of the (see amino acids 1-136 of SEQ ID NO:2) that provides a therapeutic action.

5. One skill in the art can practice this invention based on the competitive inhibition, neutralization or enhancement mechanisms described in the specifications and in the art as practiced by Bouchon et al., and Gibot et al.

6. The sequence of the ligand binding site and its application use for therapy is well disclosed in this application and combined with the common knowledge in the Art, a person has all the means to practice this invention to obtain a therapeutic action.

Taken together, the Specification coupled with knowledge in the field demonstrate the biological activity of immune modulation for all the compounds claimed and therefore enabled the claims.

Misapprehensions found in the Decision on Appeal

Issue I

The Board has agreed that the Specification are enabling and that there is no need of undue experimentation for administering a composition comprising a soluble peptide containing a portion of amino acid 1-136 of SEQ ID NO:2 to modulate an immune response in vivo (Decision p.13).

The Board disagrees with respect to peptide mimetics of SEQ ID NO:2 (Decision p. 12 and 13). This is where the Appellants believe that there is misapprehension of the term peptide mimetics by the Board. The Specification paragraph 75 is clear that peptide mimetics

are the same as peptides or functional equivalents and polypeptides. In other words, peptide mimetics or peptidomimetics are simply a synonymous of peptide functional equivalents. In that regard the Specifications paragraph 75 reads " ...the present inventors also contemplate that **structurally similar compounds** may be formulated to mimic the key portions of peptide or polypeptides of the present invention. Such compounds, which may be termed peptidomimetics, may be used in the same manner as the peptides of the invention and, hence, also are functional equivalents."

How can a peptide mimetics be structurally similar and not be the same as a peptide with a portion of amino acids 1-136 of SEQ ID NO: 2 ?

In biology, and as stated in paragraph 75, the term "mimic" means structurally similar or having the same biological active structure or sequence. On that basis, Specification paragraph 75 is directly enabled by the work that Gibot did in his report (Gibot, 2004 of record). Gibot formulated a peptide of SEQ ID NO: 2 that included enough active sequence of the key portion loop domain to obtain biological binding activity and thus immunomodulation. Gibot's peptide of 17 amino acids is a typical example of peptidomimetic or a peptide that mimics the key portion of SEQ ID NO: 2. Gibot's peptidomimetics contains a structure similar or the same sequence than a fragment of SEQ ID NO: 2 and is mimetic of the key portion of SEQ ID NO: 2 because it has ligand binding activity shown by immunomodulating activity.

Issue II

The Board brings forward first, that there is no evidence of record to indicate that the ligand for TREM-1, or its binding site within the immunoglobulin-like domain, was known at the time of the invention (Decision p. 8, FF16). Secondly, that there is no explicitly described functional equivalents or peptidomimetics in the Specification (Decision p.8, FF

17). These led to the decision that there is undue experiment necessary for enabling the invention.

First, the Appellants believe that there is misapprehension in not taking as a fact that the binding site is contained in the loop domain of the member of the immunoglobulin superfamily as presented in the Brief and Reply Brief. The Appellants assert that the presence of the binding site within the loop domain for member of the immunoglobulin superfamily is more than a claim as mentioned in Decision, FF5 and Decision p. 13. Reality is that it is a fact highly documented and accepted in the sciences of immunology since at least 30 years as documented in the both Briefs. In FF16, the Board states that there is no evidence of record to indicate that the ligand for TREM-1, or its binding site within the immunoglobulin-like domain was known at the time to the invention. It is a fact that the ligand of TREM-1 was unknown but it is a fact that its binding site was known to be within the loop domain of TREM-1 of TREM-sv as mentioned above and this knowledge goes back to the work of Edelman in 1970 and described in chapter 16 p. 427-29 of Immunology by H. N. Eisen published in 1974, (© 1974, made of record on June 21, 2006) and to Chapter 7 pp. 7.1 -7.3 of Immunology by I. M. Roitt et al. © 1989 (made of record on June 21, 2006). Both references support the fact that the binding site being in the loop domain for members of the immunoglobulin superfamily has been known for at least 11 years before filing of this invention. Thus, the location of the TREM-1 and TREM-1sv ligand-binding site to be within the loop domain was known at the time of filing and it was insisted on in the Specification paragraphs [24] and [70].

In addition, the Appellants believe that there is misapprehension of the expression "peptide mimetics" by the Board with also a misapprehension of our Specification when the Board states that "The Specification does not explicitly describe any competitive inhibitors that are "functional equivalents or "peptidomimetics"..." in Decision p. 8, FF 17.

Appellants sustain that it is not possible to list the formulation of all peptides that can be formulated that will retain biological activity. This is the reason why the Specification are written with many statements made to cover and describe all the different means by how peptides, variants and mutants can be obtained and would be like, to possess the characteristics to be subjected to the current Claims (see paragraphs 49-51, 55-63, 69-81). As long as the formulated peptides bear at least a portion of the Key portion of Sequence ID NO: 2 in their structure and display the claimed immunomodulating biological activity, they are subjected to the Claims. The test for that validation is clearly described in the Specification paragraph [179], it can be easily done by anyone skilled in the art and thus does not require undue experimentation.

Therefore, the Appellants sustains that the Specification defined in substantial details the formulation of the claimed peptides, these are enabled by the work of Bouchon et al 2001 and the work of Gibot et al 2004 and the enablement rejection must be reversed.

B. Claims 1, 3, 5, 11, 15, 16, and 40-42 are not anticipated under 35 U.S.C. 102 (e) in view of US Patent 6,420,526

Arguments of the Reply Brief are presented first to introduce the contention. Misapprehensions found in the Decision on Appeal are presented and discussed thereafter.

A basis of the rejection is the apparent similarity of the sequence SEQ ID NO: 478 and SEQ ID NO: 2 of this application. The Office's reliance on this is fundamentally misplaced for the following reasons.

Reply Brief

US Patent 6,420,526 is very vague patent. The '526 patent describes a sequence with no details in the specifications on which sequence of the molecule has a function. Functions are associated with translated proteins not with a EST DNA sequence. US Patent 6,420,526 is a multiple EST sequence patent (186 all together) containing the sequence 159 that is the subject of this objection. Sequence 159 contains 6 paragraphs for a total of a little over one page. The description in patent 526 suggests a potential use to regulate the immune response but does not describe enough to reduce to practice without undue experiments such as which part of the molecule is relevant to practice the invention. To the contrary of the present application, patent 526 description is 1) minimal with a lack of description on the molecule to use and its functional sites for someone to reduce this invention to practice. 2) There is no guidance or working evidence presented to support the rejection. 3) The present application claims are not directed to an EST sequence and related molecules as in U.S. '526 but a function of the SEQ NO: 2 molecule to modulate the immune response to treat autoimmune diseases and septic shock, which is not at all described nor reasonably ascertainable from the teachings of US '526.

Fundamentally, US '526 lacks any real disclosure that would put into the public's possession the claimed methods. US '526 merely describes an expressed sequence tag (EST) DNA sequence, among many others, including a matching sequence of. US '526 does not indicate which one or which combination of the sequence SEQ ID NO 478 being presented in seven different epitopes, must be used to produce a polypeptide usable as a protein therapeutic to modulate an immune response and whether it is an up-modulation or a down-modulation. Consequently, how can one anticipate a complete therapeutic method from such a lack of information unless it refers to the present invention? The present invention fulfills the need by clearly defining the use of as a protein therapeutic for regulating the immune response.

As the US '526 disclosure does not set forth a treatment regimen with the intended purpose of achieving the claimed effect, explicitly or inherently, the claims cannot be anticipated by the US '526 patent.

In view of the above, there can be no question that the Office's rejection based on US '526 is not sustainable and should be reversed.

Misapprehensions found in the Decision on Appeal

Issue I

The first misapprehension in this rejection is in Decision p.15, 3rd paragraph where it is being stated that Reuben's SEQ ID NO: 478 is identical to SEQ ID NO: 2. This statement is wrong. SEQ ID NO: 2 from Appellants' Specification is found in Figure 4 and is defined as being the amino acid sequence of TREM-1sv as defined in Specifications [56] and [60]. More specifically in Figure 4, TREM-1sv is the lower amino acid sequence presented. It contains only 150 amino acids because of a deletion from amino acid 136 to 200 that is coding for the transmembrane portion of TREM-1. This sequence with the deleted portion corresponds to TREM-1sv and is SEQ ID NO: 2. Reuben's SEQ ID NO: 478 contains 234 amino acids because it does not contain this deletion (see APPENDIX III, Reuben's SEQ ID NO: 478) and is therefore similar to the TREM-1 sequence or the upper sequence of amino acids presented in Figure 4. In other words, SEQ ID NO: 2 is the sequence of TREM-1sv whereas SEQ ID NO: 478 is the TREM-1 sequence. Therefore, Reuben's SEQ ID NO: 478 is not identical to the SEQ ID NO: 2 claimed by the Appellants.

Thus, rejection on the basis that the sequences of Reuben's SEQ ID NO 478 and Appellants' SEQ ID NO:2 are identical is irrelevant.

Issue II

The Appellants believe that there is misapprehension of the teaching of their invention by reducing it to the teaching of Reuben. They are providing the following additional explanations to illustrate their points.

Reuben claims a discovery based on expressed sequence tag (EST) DNA sequence. A discovery is not necessarily an invention. Reuben claims a series of EST sequences of which neither of a specific amino acid sequence with biological activity is disclosed or as to which portion is biologically active, nor is disclosed an effect to the biological function of the TREM-1 receptor. In contrast, Appellants claim invention of a therapeutic method including the use of a peptide with a specific key amino acid sequence or portion of this key sequence of SEQ ID NO: 2 for the specific application of modulating TREM-1 receptor biological activity.

Reuben teaching is based on similarity with the heavy chain of immunoglobulin (Ig) and their binding function as stated in Decision, FF19. Igs have been known to bind a wide variety of antigens long before Reuben but this is a teaching different from the one of a distinctive macrophage receptor of activation binding to its specific ligand such as the teaching of Appellant's Specification. Reuben does not teach anything in regard to the TREM-1 receptor ligand complex but rather antigens binding to antibody-like structure. Second and not the least, Reuben's Specification column 139 in "Feature of Protein Encoded by Gene No : 159 " teaches that " This gene is expressed primarily in activated neutrophil and to a lesser extent in activated T cell, monocytes, and heart." The Appellants' invention teaches that TREM-1 receptor is expressed exclusively on myeloid cells, defined as being macrophages and neutrophils (Appellant's Specification paragraph [6]) and not on T cells, defined as lymphoid cells and not on heart cells as both thought by Reuben. Exclusive expression on myeloid cells is the reason for the origin of its name TREM-1 (Triggering

Receptor Expressed on Myeloid-1) as defined by Bouchon et al., in REFERENCES of the Specification. Moreover, the Appellants teach that the specific complex TREM-1 receptor-ligand is known to trigger the TREM-1 receptor present on macrophages and to activate them, and that the binding of TREM-1sv or a peptide with the same biological binding activity to that specific TREM-1 ligand can modulate macrophage activation and thus the immune response. In contrast, Reuben teaches a molecule with the natural binding activity of Ig that can bind a large variety of antigens that may modulate the immune response but he does not teach the macrophage TREM-1 ligand complex-receptor. Moreover, to respond to Judge Scheiner question about what is the ligand of TREM-1 receptor (see Record of Oral Hearing, p. 8, lines 12-13) and as a matter of additional support for the differentiation between the teachings of each invention, there is neither data nor evidence that TREM-1 ligand is a common antigen. In fact, recent data suggest that it is a receptor expressed by platelets (Haselmayer et al. Blood 110:1029, 2007, not of record). This supports the point that our teaching about the specific TREM-1 receptor and TREM-1sv ligand binding activity is substantially different from Reuben's hypothetical molecule with Ig like binding activity for a variety of antigens and which is expressed also on T cells. As a unique substantial matter, the Appellants claim and present validation of biological activity for the loop domain or portion of it being a key sequence of SEQ ID NO: 2 and for its usage in the treatment of conditions that can benefit from capturing that specific TREM-1 receptor binding ligand with TREM-1sv or derived peptides before it reaches the myeloid expressed TREM-1 activating receptor.

In addition, the Appellants want to bring to the Board attention the fact that the Court of Appeal for the Federal Circuit has invalidated EST patents in the past as not being patentable invention. The argument that "... one skilled in the art would not know how to use the claimed ESTs because the application did not disclose a specific and substantial utility for

them" was affirmed by the CAFC. The court concluded that the claimed ESTs were no more than research intermediates that may help scientists to isolate the particular underlying protein-encoding genes and conduct further experimentation on those genes (***In re Fisher***, Fed. Cir., No. 04-1465; Sept. 7, 2005). The Appellants sustain that their Specification and Claims are the results of experimentations conducted that lead to the discovery of TREM-1sv (Specification, Figure 2 and also Gingras et al., Molecular Immunology 38:817, 2001, not of record) and they teach for that gene product and its derivative formulated peptides, application for the treatment of conditions that can benefit from capturing the specific TREM-1 receptor binding ligand.

Based on the above explanations provided in addition to those of both previous Briefs, the Appellants sustain that the rejection anticipated by Reuben must be reversed.

CONCLUSION

In view of the above remarks, Appellants request that all the remaining rejections be REVERSED.

Respectfully submitted,

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APPENDIX 1 (CLAIMS)

1. (Previously Presented) A method of modulating an immune response comprising administering to an animal, in need thereof, a composition of soluble polypeptides with at least a portion of amino acids 1 to 136 of SEQ ID NO:2 or a polypeptide mimetic thereof, in an amount effective to modulate the levels of TREM-1 and /or ligand binding activity whereby the immune response is modulated in the animal.

2. (Canceled)

3. (Previously Presented) The method of claim 1, wherein said polypeptide has at least a portion of amino acids 36 to 114 of SEQ.ID.NO:2, the whole portion of amino acids 36-114 of SEQ ID NO:2, or more than the whole portion of amino acids 36-114 of SEQ ID NO:2.

4. (Canceled)

5. (Previously Presented) The method of claim 1 or 3, wherein said immune response is an inflammatory response.

Claims 6-10. (Canceled)

11. (Previously Presented) The method of claim 1 or 3, wherein said polypeptide is admixed with a pharmaceutical carrier.

Claims 12-14 (Cancelled)

15. (Previously Presented) The method of claim 1 or 3, wherein the animal is suffering from a disease or condition is selected from the group consisting of organ transplant/rejection, bone marrow transplant/rejection, graft versus host disease, infectious disease, and an autoimmune disease.

16. (Previously Presented) The method of claim 15, wherein the disease or condition is an infectious disease and which is septic arthritis or septic shock.

17-39. (Canceled)

40. (Previously Presented) The method of claim 15, wherein the disease or condition is an autoimmune disease.

41. (Previously Presented) The method of claim 1, wherein the composition modulates LPS-induced cytokine production.

42. (Previously Presented) The method of claim 1 or 3, wherein the animal is a human.

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APPENDIX II (EVIDENCE)

1. Bouchon et al., *Nature* 410:1103, 2001 (made of record on May 27, 2004)
2. Gibot et al., J Exp Med. 200:1419, 2004 (made of record on September 12, 2005).
3. Kelker et al. *J. Mol. Biol.* 342:1237, 2004 (made of record on September 12, 2005)
4. Kelker et al. *J. Mol. Biol.* 344:1175, 2004 (made of record on September 12, 2005)
5. chapter 16 p. 427-29 of Immunology by H. N. Eisen (made of record on June 21, 2006)
6. Chapter 7 pp. 7.1 -7.3 of Immunology by I. M. Roitt et al (made of record on June 21, 2006)
7. Declaration under 37 C.F.R. § 1.132 of Marie-Claude Gingras (made of record on May 27, 2004)

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APPENDIX III Reuben's SEQ ID NO: 478

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Search Format View Sequence ID No: View Sequence

SEQ ID NO 478
LENGTH: 234
TYPE: PRT
ORGANISM: Homo sapiens
SEQUENCE: 478

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Glu Leu Arg Ala Ala Thr Lys Leu Thr Glu Glu Lys Tyr Glu Leu Lys
            20                  25                  30
Glu Gly Gln Thr Leu Asp Val Lys Cys Asp Tyr Thr Leu Glu Lys Phe
        35                  40                  45
Ala Ser Ser Gln Lys Ala Trp Gln Ile Ile Arg Asp Gly Glu Met Pro
    50                  55                  60
Lys Thr Leu Ala Cys Thr Glu Arg Pro Ser Lys Asn Ser His Pro Val
65                  70                  75                  80
Gln Val Gly Arg Ile Ile Leu Glu Asp Tyr His Asp His Gly Leu Leu
                85                  90                  95
Arg Val Arg Met Val Asn Leu Gln Val Glu Asp Ser Gly Leu Tyr Gln
            100                 105                 110
Cys Val Ile Tyr Gln Pro Pro Lys Glu Pro His Met Leu Phe Asp Arg
        115                 120                 125
Ile Arg Leu Val Val Thr Lys Gly Phe Ser Gly Thr Pro Gly Ser Asn
    130                 135                 140
Glu Asn Ser Thr Gln Asn Val Tyr Lys Ile Pro Pro Thr Thr Thr Lys
145                 150                 155                 160
Ala Leu Cys Pro Leu Tyr Thr Ser Pro Arg Thr Val Thr Gln Ala Pro
                165                 170                 175
Pro Lys Ser Thr Ala Asp Val Ser Thr Pro Asp Ser Glu Ile Asn Leu
            180                 185                 190
Thr Asn Val Thr Asp Ile Ile Arg Val Pro Val Phe Asn Ile Val Ile
        195                 200                 205
Leu Leu Ala Gly Gly Phe Leu Ser Lys Ser Leu Val Phe Ser Val Leu
    210                 215                 220
Phe Ala Val Thr Leu Arg Ser Phe Val Pro
225                 230
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